Endovascular management of acute stroke

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Stroke related to large vessel occlusion is a leading cause of disability and death worldwide. Advances in endovascular therapy to reopen occluded arteries have been shown to reduce patient disability and mortality. Expanded indications to treat patients with large vessel occlusion in the late window (>6 h from symptom onset), with basilar artery occlusion, and with large ischaemic core at presentation have enabled treatment of more patients with simplified imaging methods. Ongoing knowledge gaps include an understanding of which patients with large ischaemic infarct are more likely to benefit from endovascular therapy, the role of endovascular therapy in patients who present with low National Institutes of Health Stroke Scale scores or medium or distal vessel occlusion, and optimal management of patients with underlying intracranial atherosclerotic disease. As reperfusion can now be facilitated by intravenous thrombolysis, mechanical thrombectomy, or both, the development of cytoprotective or adjunctive drugs to slow infarct growth, enhance reperfusion, or decrease haemorrhagic risk has gained renewed interest with the hope to improve patient outcomes.

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Introduction

Endovascular therapy has transformed the management of patients with intracranial large vessel occlusion (LVO) stroke (figure 1). In 2015, several randomised trials showed the benefit of endovascular therapy compared with medical management in reducing disability in some patients, most of whom had small core infarction and presented within 6 h of symptom onset.[1] Evidence for the treatment benefit has been extended to patients presenting within 24 h of symptom onset,[2–5] patients with large ischaemic core infarct,[6–9] and patients with basilar artery occlusion.[10–12] Whether intravenous thrombolysis before endovascular therapy remains beneficial in patients with LVO has also been investigated. In parallel, the techniques used to treat LVO have evolved from use of a stent retriever to contact aspiration or combined techniques. In this Review, we distil the rationale of recent randomised trial designs and results that have proven the benefit of endovascular therapy, review current devices, and address ongoing areas under study.

Pathophysiology

When a cerebral artery is acutely occluded, the supply of vital nutrients such as oxygen and glucose to the territory irrigated by the artery is arrested, unleashing an ischaemic cascade involving glutamate-mediated excitotoxicity, oxidative stress, and inflammation.[13] Neuronal electrical function is arrested, which can manifest as an acute clinical deficit.[14] Affected areas are the area of core, which constitutes the area of tissue likely to be irreversibly injured, and the penumbra, which is the area of ischaemic tissue that is critically hypoperfused and at risk for infarction. The core is visualised as hypodensity of brain tissue on CT, reduced (<30%) cerebral blood flow compared with normal tissue on CT perfusion imaging, or hyperintensity on diffusion-weighted MRI. Although these simplified definitions have proven useful in patient selection, the vulnerability of subtypes of brain tissue varies, and the boundaries to define ischaemic core are being challenged.[15,16] The penumbra is a region with reduced blood flow that can remain viable via collaterals from leptomeningeal arteries or from the circle of Willis. The penumbra is characterised with CT perfusion or MR perfusion imaging as delayed blood flow defined by a time-to-maximum residue function of more than 6 s.[17] Clinical imaging mismatch is another concept to characterise salvageable brain tissue based on a patient presenting with a severe clinical deficit but small predicted core infarct, and might obviate the need to perform perfusion imaging.[18] The aim of intravenous thrombolysis[19] or endovascular therapy[14] is to restore blood flow to the occluded artery and thereby salvage the penumbra, or the at-risk and neurologically dysfunctional region of tissue, consequently restoring a patient's neurological function.

Despite successful angiographic reperfusion with endovascular therapy, more than half of patients with LVO do not regain functional independence.[1,20,21] Irreversible injury of brain tissue might have occurred by the time of reperfusion, explaining persisting neurological deficits. Another possible explanation is that microthrombi or platelet obstruction of capillaries might impair reperfusion of the microcirculation. The no-reflow phenomenon indicates the lack of microvascular reperfusion in the context of macrovascular reperfusion and is estimated to occur in a third of patients who have a stroke.[22,23]

Search strategy and selection criteria

The MEDLINE database was searched from Jan 1, 2015, to March 16, 2024, with the keywords "endovascular therapy", "mechanical thrombectomy", and "randomised clinical trial" (appendix p 2). Articles in the English language that were of randomised trial design were prioritised. Non-randomised studies and studies that did not compare two treatment strategies were excluded, as these were unlikely to inform evidence-based treatment. TNN and MA independently searched the literature.

See Online for appendix

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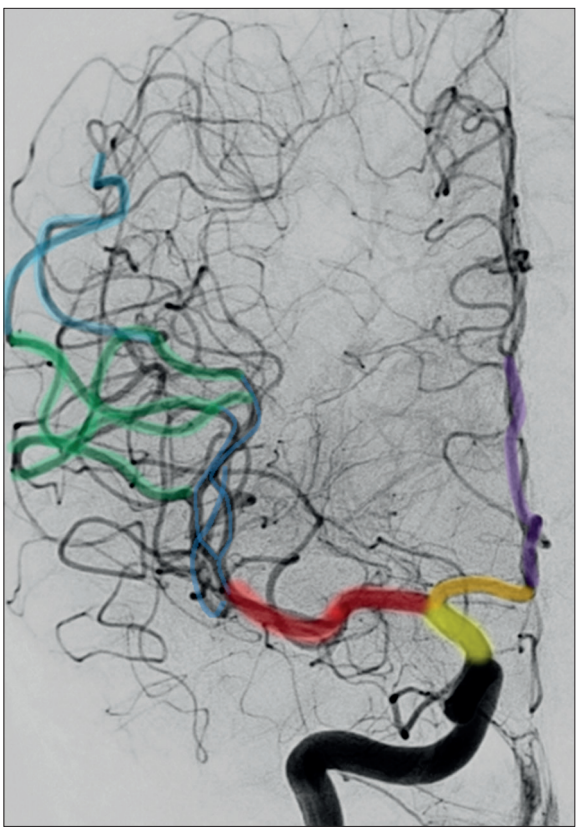

Figure 1: **Anterior posterior angiogram of the right internal carotid artery**
The right internal carotid artery is in yellow. The M1 segment is in red, the M2 segments are in blue, the M3 segments are in green, and some of the M4 segments are in light blue. The A1 segment of the left anterior cerebral artery is in orange and its A2 segment is in violet.

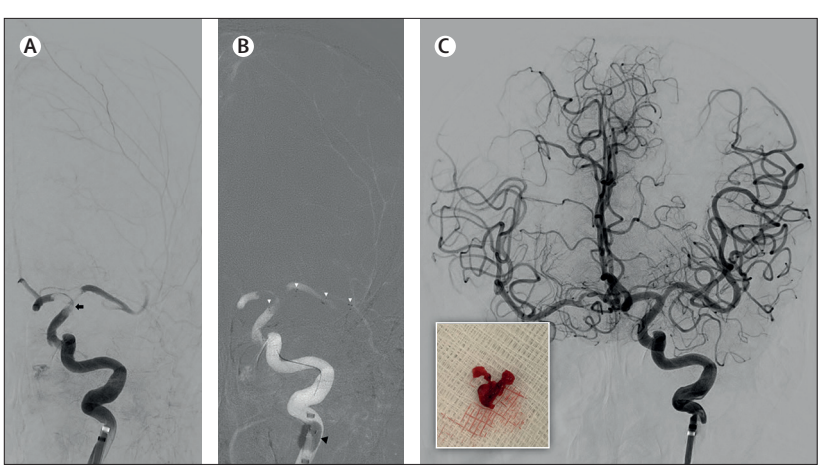

Figure 2: **Acute large vessel occlusion stroke in a patient with sudden right hemiplegia and aphasia**
(A) Cerebral angiogram of the left internal carotid artery showing acute occlusion of the left carotid terminus extending to the A1 and M1 segments of the anterior and middle cerebral arteries (black arrow). (B) Mechanical thrombectomy was performed using a stent retriever (white arrowheads) and balloon guide catheter (black arrowhead). (C) Carotid angiogram after mechanical thrombectomy with complete reperfusion of the left internal carotid artery territory. The retrieved clot is also included.

Historical overview of technical aspects of mechanical thrombectomy

Intra-arterial treatment for acute stroke was first reported in the 1950s when intra-arterial plasmin injection recanalised an acutely occluded internal carotid artery;[24] however, it was not until the 1990s that systematic investigations into intra-arterial thrombolysis began. In 1998 and 1999, the PROACT trials were the first randomised controlled trials (RCTs) to evaluate the safety and efficacy of intra-arterial treatment using pro-urokinase plus intravenous heparin versus intravenous heparin in middle cerebral artery occlusion. 40% of patients who received urokinase had a modified Rankin Scale (mRS) score of 0–2 compared with 25% of the control group (odds ratio [OR] 2·13, 95% CI 1·02–4·42; p=0·04).[25,26] In the early 2000s, clot retrieval devices emerged. The Merci Retrieval System (Concentric Medical, Mountain View, USA), using helical nitinol coils to ensnare clots, gained US Food and Drug Administration approval for arterial recanalisation in 2004,[27] followed by the Penumbra system (Penumbra, Alameda, USA) for clot aspiration.[28] Permanent intracranial stenting emerged as a viable treatment option, showing favourable angiographic patency and clinical outcomes in a prospective trial.[29,30] The introduction of stent retrievers (figure 2) heralded an improvement in reperfusion rates and clinical outcomes. Stent retrievers offered immediate flow restoration upon deployment, relying on stent radial force for thrombus penetration before retrieval. RCTs of stent retrievers, including TREVO 2 and SWIFT, showed superior reperfusion rates and improved clinical outcomes compared with the Merci retriever.[31,32]

Device-based endovascular therapy for acute ischaemic stroke was compared with standard medical therapy in three RCTs in 2013: IMS III,[33] SYNTHESIS Expansion,[34] and MR RESCUE.[35] The interventional groups comprised stent retriever devices in a minority of patients, the Merci device, and intra-arterial alteplase. The low reperfusion rates, along with patient selection criteria not mandating CT angiography to detect LVO for randomisation, probably contributed to the trials' inability to show superior clinical outcomes with endovascular therapy.

Randomised trials using the new generation of devices and unequivocally confirming the benefit of endovascular therapy over best medical treatment in selected patients revolutionised management of stroke in 2014–15. These trials used an angiographic rating scale, the modified treatment in cerebral infarction (mTICI), that visually estimated the extent to which the target downstream territory was reperfused (appendix p 3).[36,37] Angiographic reperfusion rates (mTICI grade 2b–3) reached up to 88% in the SWIFT PRIME trial.[38] Stent retrievers were predominantly used in these trials. Two subsequent RCTs showed that contact aspiration was non-inferior to stent retrievers for treatment of acute anterior circulation LVO stroke, although crossover from direct aspiration to stent retriever occurred in 21% of patients in the COMPASS

trial, and rescue treatment after first-line aspiration occurred in 33% of patients in the ASTER trial.[39,40]

Advancements in technique since 2015 have also improved the technical and clinical effectiveness of endovascular therapy. Although some retrospective studies suggested the superiority of combined contact aspiration and stent retriever thrombectomy (ie, the Solumbra technique), one RCT did not show an increase in reperfusion rates compared with the stent retriever technique alone.[41] Balloon guide catheters facilitating flow arrest and reversal while reducing distal emboli risk have been associated with higher revascularisation rates, shorter procedure times, and improved clinical outcomes compared with conventional guide catheter; two RCTs studying this are ongoing (NCT05592054 and NCT05020795).[42–44] The development of large inner diameter 0·088 inch intracranial access aspiration catheters with improved trackability enabled large-bore intracranial access and resulted in high aspiration force and high first-pass effect.[45] In patients with difficult aortic arch anatomy,[46] radial artery approach facilitated intracranial access. One RCT showed non-inferiority of

	Participants (n)	Population	Time window (h)	Imaging selection	Comparison	Primary outcome at 90 days	Result	EVT *vs* MM
Early time window (0–8 h)								
MR CLEAN[48]	500	LVO ICA, M1, or M2	0–6	NCCT and CTA	EVT *vs* MM	Ordinal mRS	Adjusted common OR 1·67, 95% CI 1·21–2·30	mRS 0–2 (90 days) 32·6% *vs* 19·1%
ESCAPE[49]*	316	LVO ICA, M1, or M2	0–12	NCCT, CTA (multiphase preferred), ASPECTS 6–10, and moderate to good collaterals	EVT *vs* MM	Ordinal mRS	Common OR 2·6, 95% CI 1·7–3·8; p<0·001	mRS 0–2 (90 days) 53·0% *vs* 29·3%; p<0·001
SWIFT PRIME[38]*	196	LVO ICA, M1, and receiving intravenous alteplase	0–6	CTP initially, then NCCT permitted after 71 patients enrolled	EVT (Solitaire) *vs* MM	Ordinal mRS	Risk ratio 1·70, 95% CI 1·23–2·33; p<0·001	mRS 0–2 (90 days) 60% *vs* 35%; p<0·001
EXTEND IA[50]	70	LVO ICA, M1, or M2, and receiving intravenous alteplase	0–6	CTP core <70 mL and salvageable tissue	EVT *vs* MM	Reperfusion 24 h, Early Neurological Improvement†	Reperfusion 24 h 100% *vs* 37%, p<0·001; ENI 80% *vs* 37%, p=0·002	mRS 0–2 (90 days) 71% *vs* 40%; p=0·01
REVASCAT[51]	206	LVO anterior circulation	0–8	NCCT: ASPECTS ≥7 or DWI: ASPECTS ≥6	EVT (Solitaire) *vs* MM	Ordinal mRS	Adjusted OR 1·7, 95% CI 1·05–2·8	mRS 0–2 (90 days) 43·7% *vs* 28·2%
THRACE[52]	414	LVO ICA, M1, or superior third basilar artery	0–5	Not specified	EVT *vs* MM	mRS 0–2	OR 1·55, 95% CI 1·05–2·30, p=0·028	mRS 0–2 (90 days) 53% *vs* 42%; p=0·03
PISTE[53]	65	LVO ICA, M1, or single M2, and receiving intravenous alteplase	0–5·5	No extensive or established hypodensity	EVT *vs* MM	mRS 0–2	Adjusted OR 2·12, 95% CI 0·65–6·94, p=0·20	mRS 0–2 (90 days) 51% *vs* 40%; p=0·20
EASI[54]*	77	LVO anterior or posterior circulation	0–5	Clinical imaging mismatch	EVT *vs* MM	mRS 0–2	NA	mRS 0–2 (90 days) 50% *vs* 37·8%; p=0·36
RESILIENT[55]*	221	LVO ICA or M1	0–8	NCCT: ASPECTS >6, DWI: ASPECTS >5 and no collaterals on CTA, or CTP	EVT *vs* MM	Ordinal mRS	Common OR 2·28, 95% CI 1·41–3·69, p=0·001	mRS 0–2 (90 days) 35·1% *vs* 20·0%
Late time window (6–24 h)								
DAWN[3]*	206	LVO ICA or MCA	6–24	CTP and MRI	EVT *vs* MM	Utility-weighted mRS	5·5 *vs* 3·4, posterior probability of superiority >0·999	mRS 0–2 (90 days) 49% *vs* 13%
DEFUSE3[4]*	182	LVO ICA or MCA	6–16	CTP and MRI	EVT *vs* MM	Ordinal mRS	OR 2·77, 95% CI 1·63–4·70; p<0·001	mRS 0–2 (90 days) 45% *vs* 17%
MR CLEAN LATE[5]	502	LVO ICA, M1, or M2	6–24	Hypodensity less than a third of MCA territory, CT, and CTA collaterals	EVT *vs* MM	Ordinal mRS	Common OR 1·67, 95% CI 1·20–2·32	mRS 0–2 (90 days) 39% *vs* 34%
Basilar artery occlusion								
BASICS[56]	300	BAO	0–6	NCCT	EVT *vs* MM	mRS 0–3	Risk ratio 1·18, 95% CI 0·92–1·50; p=0·19	mRS 0–3 (90 days) 44% *vs* 38%
BEST[57]	131	BAO	0–8	NCCT	EVT *vs* MM	mRS 0–3	Adjusted OR 1·74 0·81–3·74; p=0·23	mRS 0–3 (90 days) 42% *vs* 32%
ATTENTION[10]	340	BAO	0–12	NCCT or CTP	EVT *vs* MM	mRS 0–3	Adjusted rate ratio 2·06, 95% CI 1·46–2·91; p<0·001	mRS 0–3 (90 days) 46% *vs* 23%
BAOCHE[11]	217	BAO	6–24	NCCT or CTP	EVT *vs* MM	mRS 0–3	Adjusted rate ratio 1·81, 95% CI 1·26–2·60; p<0·001	mRS 0–3 (90 days) 46% *vs* 24%

(Table 1 continues on next page)

	Participants (n)	Population	Time window (h)	Imaging selection	Comparison	Primary outcome at 90 days	Result	EVT *vs* MM
(Continued from previous page)								
Large core								
RESCUE JAPAN LIMIT[6]	203	LVO ICA or M1	0–24	ASPECTS 3–5 on CT or MRI <6 h and no FLAIR signal 6–24 h	EVT *vs* MM	mRS 0–3	Relative risk 2·43, 95% CI 1·35–4·37, p=0·002	mRS 0–3 (90 days) 31·0% *vs* 12·7%
ANGEL ASPECT[7]*	456	LVO ICA or MCA	0–24	ASPECTS 3–5 or ASPECTS 0–2 with infarct core 70–100 mL	EVT *vs* MM	Ordinal mRS	Generalised OR 1·37, 95% CI 1·11–1·69, p=0·004	mRS 0–3 (90 days) 47·0% *vs* 33·3%
SELECT2[8]*	352	LVO ICA or M1	0–24	ASPECTS 3–5 or ischaemic core ≥50 mL on CTP or MRI	EVT *vs* MM	Ordinal mRS	Generalised OR 1·51, 95% CI 1·20–1·89, p<0·001	mRS 0–3 (90 days) 37·9% *vs* 18·7%; mRS 0–2 (90 days) 20% *vs* 7%
TESLA[58]	299	NCCT ASPECTS 2–5	0–24	NCCT ASPECTS 2–5	EVT *vs* MM	Utility-weighted mRS	2·93 (SD 3·39) *vs* 2·27 (SD 2·98); adjusted difference 0·63 (95% credible interval −0·09 to 1·34), posterior probability of superiority 0·96	mRS 0–3 (90 days) 30% *vs* 20%
LASTE[59]*	333	LVO ICA or M1	0–6·5 (or normal FLAIR if unknown)	ASPECTS 0–5 NCCT or DWI, or ASPECTS 4 or 5 in patients aged 80 years or older	EVT *vs* MM	Ordinal mRS	Generalised OR 1·63, 95% CI 1·29–2·06, p<0·0001	mRS 0–3 (90 days) 33·5% *vs* 12·2%
TENSION[60]*	253	LVO ICA or M1	0–12	NCCT or DWI ASPECTS 3–5	EVT *vs* MM	Ordinal mRS	Adjusted common OR 2·58, 95% CI 1·60–4·15, p=0·0001	mRS 0–3 (90 days) 31% *vs* 13%

ASPECTS=Alberta Stroke Program Early CT Score. BAO=basilar artery occlusion. CTA=CT angiography. CTP=CT perfusion. DWI=diffusion-weighted imaging. ENI=early neurological improvement. EVT=endovascular therapy. FLAIR=fluid attenuated inversion recovery. ICA=internal carotid artery. LVO=large vessel occlusion. MCA=middle cerebral artery. MM=medical management. mRS=modified Rankin Scale. NA=not available. NCCT=non-contrast computed tomography. OR=odds ratio. *Stopped early. †EXTEND IA: ENI (ie, ≥8-point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 3).

Table 1: **Randomised trials of endovascular therapy versus medical management for large vessel occlusion stroke**

radial access compared with femoral access in patients receiving endovascular therapy for the primary outcome of final reperfusion.[47]

Small core, early window

The randomised trials of 2015–17 showed that, in patients with anterior circulation proximal LVO and moderate-to-severe stroke, endovascular therapy reduced the odds of disability at 3 months compared with medical management (adjusted common OR 2·49, 95% CI 1·76–3·53; p<0·0001; table 1).[1] The number needed to treat to prevent 3-month disability for one patient was 3.[1] Trials that used liberal selection criteria (without restriction on a minimum Alberta Stroke Program Early CT Score [ASPECTS] or baseline National Institutes for Health Stroke Scale [NIHSS] score), such as MR CLEAN,[48] showed treatment benefit across a broad range of patient presentations (mRS 0–2 adjusted common OR 1·67, 95% CI 1·21–2·30), although with smaller effect size compared with trials with more stringent eligibility criteria (eg, EXTEND-IA and SWIFT PRIME).[38,50] The medical groups of the EXTEND-IA and SWIFT PRIME trials had 90-day mRS outcomes that were higher than that of the endovascular therapy arm of MR CLEAN, which suggests that these trials had selective eligibility criteria of patients who were probably going to do well. With regard to safety, the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke (HERMES) trials meta-analysis of five early trials showed that the risk of symptomatic intracranial haemorrhage was similar between the two groups. The benefit of endovascular therapy was preserved across subgroups, including patients older than 80 years, patients with proximal and dominant M2 occlusions, patients who received intravenous thrombolysis, and possibly patients with low ASPECTS (0–4), based on a small sample (n=126).[1,61,62]

Small core, late window

In 2018, the benefit of endovascular therapy was extended to patients presenting in the 6–24 h window, shifting the selection paradigm to the subset of patients with higher volumes of penumbra or clinical severity relative to predicted core infarction. The Diffusion-Weighted Imaging or CT Perfusion Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial showed that in patients who presented within 6–24 h of symptom onset with anterior circulation LVO with clinical imaging mismatch, endovascular therapy was associated with higher functional independence (mRS 0–2 49% *vs* 13%; adjusted difference 33%, 95% credible interval 21–44) and lower disability compared with medical management.[3] The

Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE3) trial reported that in patients presenting within 6–16 h of onset with anterior circulation LVO with perfusion imaging mismatch, a favourable shift occurred in 90-day mRS outcomes (OR 2·77, 95% CI 1·63–4·70; p<0·001) and functional independence improved (mRS 0–2 45% *vs* 17%; p<0·001).[4]

The large treatment effects observed in the DAWN and DEFUSE3 trials suggest that their eligibility criteria were restrictive.[63] Advanced imaging modalities such as CT perfusion and MRI were required to select patients into the late window in major guidelines.[64,65] Other guidelines are not as restrictive[66] based on liberal interpretations of the evidence, probably driven by advanced imaging not being readily available in many hospitals, particularly in primary stroke centres and in low-income or middle-income countries.[67,68] Hence, the use of non-contrast CT (NCCT) as imaging triage modality alone for endovascular therapy has been examined in several studies, showing comparable results to patients being selected with CT perfusion or MRI,[69–72] and better outcomes compared with patients with anterior LVO who are medically managed.[73,74] Time to endovascular therapy treatment was 20 min faster in patients selected by NCCT compared with CT perfusion or MRI in the 6–24 h window.[69] Imaging selection with NCCT and CT angiography alone reduces the use of iodinated contrast depending on scanner protocols[16,75] and radiation exposure with CT perfusion.

The MR CLEAN LATE trial expanded patient eligibility for endovascular therapy in the 6–24 h window using simpler imaging.[5] The trial randomly assigned patients with anterior circulation LVO who were ineligible for DAWN and DEFUSE3 between endovascular therapy or medical management using NCCT and CT angiography collaterals. Patients with no collaterals on CT angiography were excluded. The median mRS score at 90 days was lower in the endovascular therapy group than in the control group (3 [IQR 2–5] *vs* 4 [2–6]), and there was a shift towards better outcomes on the mRS for endovascular therapy (adjusted common OR 1·67 [95% CI 1·20–2·32]). Symptomatic intracranial haemorrhage occurred more often in the endovascular therapy group than the control group (17 [7%] *vs* 4 [2%]; adjusted odds ratio 4·59, 95% CI 1·49–14·10).[5]

Large core

Patients with an anterior circulation large ischaemic core stroke comprise an estimated 10–15% of an unselected population in the 24 h time window.[76] Reperfusion haemorrhage and the development of malignant cerebral oedema have been the concerns of reperfusion in patients with a large ischaemic core.[77] Six large core trials have been completed, with different patient and imaging selection criteria (table 1).

Among patients with ASPECTS of 3–5 by CT or MRI within 6 h of symptom onset, or with MRI absence of fluid-attenuated inversion recovery signal from 6–24 h of symptom onset, the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT) randomly assigned patients to endovascular treatment or medical management.[6] The primary outcome of mRS score 0–3 favoured patients treated with endovascular therapy versus medical management (31·0% *vs* 12·7%; relative risk 2·43, 95% CI 1·35–4·37; p=0·002). 86% of patients in the RESCUE-Japan LIMIT trial were selected by MRI, limiting the generalisability of this trial's findings as most hospitals do not have access to acute MRI.[6,67]

Using either ASPECTS of 3–5 (no volume limit) or ASPECTS of 0–2 with 70–100 mL volume within 24 h of onset, the randomised Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core (ANGEL-ASPECT) trial was stopped early when an interim analysis showed clinical benefit. A shift occurred in ordinal mRS scores in favour of endovascular therapy versus medical management (generalised OR 1·37, 95% CI 1·11–1·69; p=0·004), despite a higher rate of symptomatic intracranial haemorrhage in the endovascular therapy group (6·1% *vs* 2·7%).

Randomising patients with an ASPECTS of 3–5 or a core volume of more than 50 mL on CT perfusion or MRI up to 24 h from symptom onset, the Randomised Controlled Trial to Optimise Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2) was stopped early for efficacy of the primary outcome of ordinal mRS scores, in favour of endovascular therapy compared with medical management (generalised OR 1·51, 95% CI 1·20–1·89; p<0·001).[8,78] Subgroup analysis of SELECT2 showed treatment effect across subgroups, including in the presence or absence of perfusion mismatch, and with very large infarct core volumes of either 100 mL or more or 150 mL or more, although the number of patients enrolled without mismatch or with more than 150 mL volume was small.[79]

Randomising patients with ASPECTS of 3–5 up to 12 h from symptom onset, the Efficacy and Safety of Thrombectomy in Stroke with Extended Lesion and Extended Time Window (TENSION) trial was stopped early at interim analysis. Using mostly CT selection (82%), the trial showed a shift to better outcome by ordinal mRS scores (adjusted common OR 2·58, 95% CI 1·60–4·15; p=0·0001) and lower mortality (hazard ratio 0·67, 95% CI 0·46–0·98; p=0·038) with endovascular therapy compared with medical management, without an increase in the rate of symptomatic intracranial haemorrhage.[60] Enrolling patients with ASPECTS of 2–5 by NCCT alone up to 24 h from symptom onset, preliminary results of the Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (TESLA) trial fell short of the trial's primary outcome of utility-weighted mRS scores (mean 2·93 *vs* 2·27, posterior probability of superiority 0·957).[58]

Finally, in randomly assigned patients with ASPECTS of 0–5 presenting in the 7 h window, the Large Stroke

Therapy Evaluation (LASTE) trial showed improved outcomes in the endovascular therapy group compared with the medical management group by ordinal mRS scores (generalised OR 1·63, 95% CI 1·29–2·06; p<0·0001). The trial used mostly MRI-based selection (84% of patients).[59] Altogether, these six trials support the treatment of subsets of patients with large ischaemic cores up to the 24 h window.[9] Although all large core trials reported core size, reporting of the penumbra volumes was less common, and few patients without the presence of mismatch were enrolled.[79,80,81] Additional individual patient analysis stratifying by ASPECTS, degree of hypodensity, presence or absence of mismatch, and patient factors including time to presentation will be important to understand the endovascular therapy treatment effect across subgroups.

Basilar artery occlusion

Basilar artery occlusion (BAO) was among the first clinical syndromes to inspire the development of intra-arterial thrombolytic therapy for acute stroke.[82,83] The clinical presentation of BAO is vast, and patients can present any component or combination of symptoms that include dysarthria, dysphagia, cranial nerve deficit, sensory deficit, hemiplegia, and progressing to a locked-in syndrome.[84] An estimated 60–80% of patients with BAO do not regain independence with medical management.[85] Nonetheless, BAO was the last of the LVO locations with completed RCTs to show the efficacy of endovascular therapy.

Two early trials, BASICS and BEST, showed a neutral effect of endovascular therapy.[56,57] Formidable challenges in patient recruitment occurred in both trials, including patient crossovers in the BEST trial and lack of consecutive enrolment. Enrolment of patients with mild BAO (ie, NIHSS score <10) in BASICS might have explained the absence of treatment effect.[86] A better-than-expected rate of favourable outcomes in the medical group of the BASICS trial (mRS 0–3 38%), with nearly 80% of patients treated with intravenous thrombolysis, also suggested relative benefit associated with intravenous thrombolysis for the posterior circulation compared with the anterior circulation.[56] Despite neutral results, physicians believed that patients with BAO should be referred for endovascular therapy, according to an international survey.[87,88] The belief that additional BAO RCTs are needed was higher among stroke physicians from China than from other countries.[89] The ATTENTION trial emphasised consecutive enrolment of patients with BAO and showed that in patients with BAO who presented within 12 h of symptom onset with an NIHSS score of 10 or higher, endovascular therapy was associated with a greater likelihood of good outcome than medical management (mRS 0–3 46% *vs* 23%; adjusted rate ratio 2·06, 95% CI 1·46–2·91; p<0·001).[10] The BAOCHE trial randomly assigned patients with BAO presenting within 6–24 h of symptom onset with NIHSS score of 6 or higher, and showed superiority of endovascular therapy compared with medical management (mRS 0–3 46% *vs* 24%; adjusted rate ratio 1·81, 95% CI 1·26–2·60; p<0·001).[11] Altogether, meta-analyses of these RCTs have shown a treatment effect in favour of endovascular therapy in most patients with moderate-to-severe BAO and less certainty for patients with mild deficit (NIHSS score <10).[12]

Bridging thrombolysis

In the landmark trials showing the benefit of endovascular therapy of acute stroke in patients with LVO, intravenous thrombolysis was given to all patients who were eligible for thrombolytics.[1] Therefore, administration of intravenous thrombolysis before endovascular therapy is recommended by guidelines.[64,65,90] The value of intravenous thrombolysis in combination with endovascular therapy in patients directly admitted to endovascular therapy centres has been questioned.[91,92] Although intravenous thrombolysis in addition to endovascular therapy might increase the overall postinterventional reperfusion rate, it has a rapidly decreasing efficacy over time and has insufficient preinterventional reperfusion rates.[91,93] Worldwide shortages of thrombolytics and the cost of thrombolysis have increased the relevance of this topic.

Six randomised clinical trials assessed whether endovascular therapy alone is non-inferior to intravenous thrombolysis followed by endovascular therapy within 4·5 h of symptom onset in people with mostly anterior LVO stroke and no contraindications to intravenous thrombolysis, presenting directly to an endovascular therapy centre. Trials that showed non-inferiority of endovascular therapy alone had generous non-inferiority margins.[94,95] An individual participant (n=2313) meta-analysis of these six trials (IRIS) did not establish non-inferiority of endovascular therapy alone compared with intravenous thrombolysis plus endovascular therapy in patients presenting directly at endovascular centres: the median mRS score at 90 days was 3 (IQR 1–5) in the endovascular therapy alone group and 2 (IQR 1–4) in the intravenous thrombolysis plus endovascular therapy group (adjusted common OR 0·89, 95% CI 0·76–1·04).[96] Symptomatic intracranial haemorrhage and mortality rates did not differ. A clinically relevant effect when omitting intravenous thrombolysis in patients having endovascular therapy cannot be excluded, but the benefit of intravenous thrombolysis is likely to be small for those presenting to endovascular therapy-capable hospitals. Furthermore, the treatment effect of intravenous thrombolysis plus thrombectomy compared with thrombectomy alone in patients presenting at thrombectomy-capable stroke centres is time-dependent, such that earlier treatment showed more treatment benefit.[97] Patients presenting with LVO at non-endovascular therapy-capable hospitals should, however, be treated with intravenous thrombolysis. As tenecteplase becomes increasingly used, it might offer incremental benefit compared with alteplase.[19,98,99]

Intracranial atherosclerotic disease LVO

Intracranial atherosclerotic disease (ICAD)-related LVO accounts for 10–65% of LVO stroke, and is more frequent in people with Asian, Hispanic, or Black ethnicities.[21,100–102] The presence of underlying ICAD is associated both with a greater than 3-fold risk of reocclusion and with procedural challenges due to vessel wall disruption, when compared with patients who do not have large vessel atherosclerosis (OR 3·44, 95% CI 1·12–10·61; I^2=50%; figure 3).[103]

Antiplatelet therapy is usually initiated before, during, or after endovascular therapy, to prevent reocclusion and thrombotic complications. In practice, antiplatelet preparatory treatment can be challenging because ICAD is difficult to predict before endovascular therapy. Glycoprotein IIb and IIIa inhibitors are increasingly used in the periprocedural period for patients with ICAD-related LVO, although evidence remains poor.[104,105] Endovascular Treatment With Versus Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT), a randomised, placebo-controlled trial, showed that intravenous tirofiban administered before endovascular therapy did not improve clinical outcomes.[106] Subgroup analysis of patients in the RESCUE BT trial with ICAD-related LVO showed that tirofiban improved neurological outcomes by reducing the number of thrombectomy attempts but did not reduce reocclusion rates.[107]

Similar to other types of LVO stroke, patients with ICAD-related LVO stroke might also benefit from endovascular therapy with a stent retriever or contact aspiration (or both); however, up to 52% of patients with ICAD-related LVO stroke have recanalisation failure after mechanical thrombectomy alone and require rescue treatment with angioplasty, stenting, or intra-arterial medication to have successful reperfusion.[107,108] A meta-analysis showed that patients with ICAD-related LVO who received rescue therapy had better outcomes and lower mortality without increasing symptomatic intracranial haemorrhage compared with patients who did not receive rescue therapy.[109] Some studies suggested that primary angioplasty or primary stenting can yield similar or better outcomes to rescue angioplasty after mechanical thrombectomy.[110–112] Other studies have suggested that adequate reperfusion, rather than angioplasty, stenting, or complete and sustained reperfusion, should be prioritised, because neurological deterioration can occur despite improved recanalisation with angioplasty or stenting (or both) due to perforator occlusion, distal embolism, and a longer procedure time. Therefore, patient selection is crucial, and rescue angioplasty and stenting should be restricted to patients at high risk of reocclusion despite antiplatelet agents.

The ANGEL-REBOOT randomised trial of patients with unsuccessful recanalisation or patients at risk of reocclusion after thrombectomy showed that balloon angioplasty or stenting did not improve 90-day clinical outcome compared with standard therapy.[113] This is probably explained by the fact that the control group had high recanalisation rates, and there was a high use of tirofiban in both the interventional and control group. Trials of rescue stenting or angioplasty (or both) are ongoing with the RESCUE ICAS,[114] ICARUS,[115] and PISTAR[116] trials.

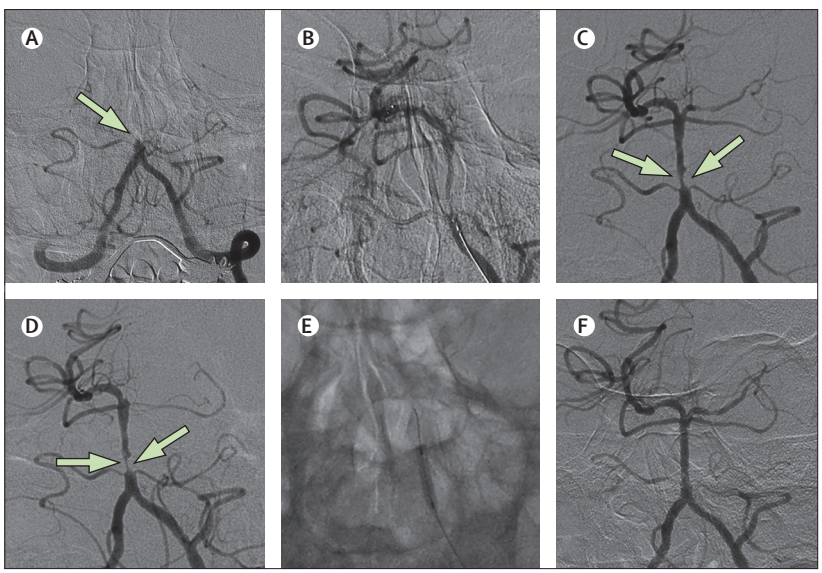

Figure 3: **Intracranial atherosclerotic-related basilar artery occlusion**
A man aged 67 years presented with slurred speech and left hemiparesis (with a National Institutes of Health Stroke Scale score of 23). (A) Angiography showed proximal occlusion of the basilar artery (arrow). (B) Mechanical thrombectomy was performed with the Solitaire stent retriever (Medtronic, Minneapolis, MN, USA). (C) After thrombus removal, there was a focal severe stenosis (arrows). (D) The stenosis worsened after continuous infusion of tirofiban over 10 min (arrows). (E) The balloon was inflated in the basilar artery but reoccluded. (F) Final recanalisation was completed with an Apollo stent deployed.

Periprocedural antithrombotics

The Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands-Med (MR CLEAN-MED) of patients having endovascular therapy compared 300 mg intravenous aspirin with no intravenous aspirin and 5000 units intravenous heparin followed by a 6 h infusion with no intravenous heparin administered after groin puncture. The trial was stopped early because of a higher rate of symptomatic intracranial haemorrhage in the interventional group compared with the control group (intravenous aspirin 14% *vs* 7%, adjusted OR [aOR] 1·95, 95% CI 1·13–3·35; intravenous heparin 13% *vs* 7%, aOR 1·98, 95% CI 1·14–3·46).[117] These data suggest that routine intravenous heparin or intravenous aspirin should be avoided in the periprocedural endovascular therapy period. However, periprocedural antiplatelet can be considered on a case-by-case basis in patients with ICAD-related LVO, with tandem lesion LVO, or who have acute stenting considering the high risk of reocclusion.[104]

The Chemical Optimization of Cerebral Embolectomy (CHOICE) trial was a phase 2b RCT of patients who had had successful reperfusion (expanded treatment in

cerebral infarction grade 2b50–3) to receive 0·225 mg/kg intra-arterial alteplase (maximum dose 22·5 mg) versus placebo. The rationale of adjunctive thrombolysis after successful endovascular therapy was to test whether this treatment could improve outcomes by recanalising occlusions in visually occluded distal arteries or in the non-visualised microcirculation. Of 121 randomly assigned patients, better neurological outcomes were observed in the interventional group (mRS 0–1 59·0% *vs* 40·4%; adjusted risk difference 18·4%, 95% CI 0·3–36·4%; p=0·047).[118] The use of adjunct intra-arterial thrombolytic after successful reperfusion is currently being tested across several RCTs (table 2).[120,121]

Medium or distal vessel occlusion

Medium or distal vessel occlusions (MeVOs) are defined as visible arterial occlusions that occur distal to an LVO, comprising the M3, M4, and some M2 segments of the middle cerebral artery; P1, P2, and P3 segments of the posterior cerebral artery; the fetal posterior cerebral artery;[122] or A1 and A2 segments of the anterior cerebral artery. A MeVO can be considered as a primary occlusion if the occlusion first lodged at the index artery, or a secondary occlusion if the occlusion migrated spontaneously (eg, from CT angiography to digital subtraction angiography) or embolised into a downstream or new territory after a thrombectomy pass (eg, an LVO becomes a MeVO). The classification of M2 occlusion as LVO versus MeVO depends on its calibre and the M2 segment in which the occlusion is lodged. A proximal dominant M2 branch occlusion would be considered an LVO, whereas a non-dominant branch, co-dominant branch, or distal M2 occlusion would be a MeVO.

Although patients who present with MeVO tend to have less severe clinical deficits than patients with LVO, a third to a half of patients with MeVO might not regain functional independence despite medical or endovascular management.[123,124] Occlusions in distal arteries involve smaller calibre arteries, along with an adjustment in endovascular therapy technique to use smaller aspiration catheters or stent retrievers for clot retrieval, or intra-arterial thrombolysis.[125–127] Arterial tortuosity is another consideration with distal navigation. Hence, the benefit–risk ratio should be considered, particularly in light of the fact that clots in more distal locations, with their reduced clot burden, might be more responsive to intravenous thrombolysis.[128] Several trials are testing whether endovascular therapy with a device or intra-arterial thrombolytic therapy is superior to medical management in patients with MeVO or incomplete reperfusion after thrombectomy (table 2).

Adjunctive therapy

After 40 years of unsuccessful attempts to show a benefit of neuroprotective agents from bench to human trials of ischaemic stroke, neuroprotection has gained renewed interest as adjunctive therapy to endovascular therapy due to the ability to reperfuse an occluded artery.[13] With reperfusion, a neuroprotectant drug can reach at-risk tissue.[129] Mechanisms by which a neuroprotection agent can act include slowing or freezing infarct growth, antiapoptosis,[130] anti-inflammatory effect,[129,130] anti-oxidation,[130] stimulating collateral flow, protecting the microcirculation, limiting haemorrhagic conversion of ischaemic infarction, and limiting cerebral oedema. Hence, a drug with pleiotropic effects would be ideal for clinical practice.

Nerinetide is a peptide molecule that inhibits excitotoxic glutamate signalling via disruption of the synaptic folding protein PSD-95.[131] The ESCAPE NA-1 trial tested a single intravenous dose of nerinetide (NoNO, Toronto, ON, Canada) versus placebo in patients presenting within 12 h of symptom onset with LVO before having endovascular therapy. Although the overall results were neutral, subgroup analysis of patients who did not receive intravenous alteplase showed better outcomes in patients who had received nerinetide (mRS 0–2 59·3% *vs* 49·8%; adjusted risk ratio 1·18, 95% CI 1·01–1·38).[131] Animal studies showed that nerinetide is cleaved by plasmin, and alteplase therefore negates the effect of nerinetide on infarct volume as shown in rat models.[132] Notwithstanding, preliminary results of the ESCAPE NEXT trial (NCT04462536) did not show benefit of nerinetide in patients with LVO who presented within 12 h of symptom onset and who did not receive alteplase, whereas preliminary results of the exploratory FRONTIER trial (NCT02315443) suggest potential benefit of nerinetide when administered by paramedics early in the prehospital phase.

ApTOLL (aptaTargets, Madrid, Spain), a DNA aptamer, is an antagonist at toll-like receptor 4 involved in the immune and inflammatory responses. APRIL, a phase 1b/2a randomised placebo-controlled clinical trial, showed that early (ie, within 0–6 h of symptom onset) administration of 0·2 mg/kg ApTOLL intravenously before endovascular therapy in patients with anterior circulation LVO lowered mortality and disability compared with placebo.[129] These findings require confirmation in larger trials.

DL-3-n-butylphthalide (NBP; Shijiazhuang Pharmaceutical, Shijiazhuang, China) is a compound extracted from the seeds of Chinese celery with several potential mechanisms of action including anti-inflammation, antioxidation, and antiapoptosis. The phase 3 Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) trial randomly assigned patients with acute ischaemic stroke within 6 h of symptom onset who had received intravenous thrombolysis, endovascular therapy, or both, to NBP (intravenous NBP for 2 weeks, then oral NBP for 10 weeks) or placebo. A higher proportion of patients had 90-day favourable functional outcomes (mRS 0–2 56·7% *vs* 44·0%; OR 1·70, 95% CI 1·35–2·14; p<0·001)

	Population	Vessel occlusion	Time window	Comparison	Primary outcome
Medium or distal vessel occlusion: EVT *vs* medical management with device					
DISCOUNT (NCT05030142)	NIHSS ≥5	Distal M2 or M3; A1, A2, or A3; P1, P2, or P3	≤6 h	MM *vs* EVT (Trevo, Catchview Mini, Tigertriver 13, or pReset Lite)	90-day mRS 0–2
DISTAL (NCT05029414)	NIHSS ≥4 or disabling symptoms	Co-dominant or non-dominant M2, M3, or M4; A1, A2, or A3; P1, P2, or P3	≤24 h	MM *vs* EVT (all Conformité Européenne-certified devices)	90-day mRS
DISTALS (NCT05152524)	NIHSS 4–24 or 2–24 with aphasia or hemianopia	Distal vessel diameter ≥1·5 mm	≤24 h	MM *vs* EVT (Tigertriever)	Successful reperfusion without symptomatic intracranial haemorrhage
DUSK (NCT05983757)	NIHSS >5 or NIHSS 3–5 with disabling symptoms	Co-dominant or non-dominant M2, M3, or M4; A1, A2, or A3; P1, P2, or P3	<12 h	MM *vs* EVT (Trevo+Vecta 46 or CAT5 distal access catheter)	90-day mRS
ESCAPE MeVO (NCT05151172)	NIHSS ≥5 or NIHSS 3–5 with disabling deficit	M2 or M3, A2 or A3, P2 or P3	<12 h	MM *vs* EVT (Solitaire)	90-day mRS
Frontier AP (ACTRN12621001746820)	NIHSS ≥5 or dysphasia if NIHSS <5	M2 or M3; A1 or A2	<9 h	MM *vs* EVT (Solitaire)	90-day mRS
ORIENTAL MeVO (NCT06146790)	NIHSS ≥6	Co-dominant or non-dominant M2 or M3; A1, A2, or A3; P1, P2, or P3	<12 h	MM *vs* EVT (China Food and Drug Administration-approved devices)	90-day mRS
Medium or distal vessel occlusion: EVT *vs* medical management with thrombolytic therapy					
ALLY (phase 2; NCT05172934)	LVO with incomplete reperfusion eTICI 2b–2c	ICA M1 or M2	<24 h	Intra-arterial tenecteplase (single-arm pilot)	Any intracranial haemorrhage or neurological deterioration
RESCUE TNK[119] (phase 2/3; NCT05657470)	Primary MeVO or secondary MeVO	M2–3, A1–3, P1–3, PICA, AICA, or SCA	NA	MM *vs* 0·2–0·3 mg/min intra-arterial tenecteplase for 20–30 min	eTICI 2b67–3 in territory of MeVO
TECNO (NCT05499832)	LVO with incomplete reperfusion eTICI 2b–3	ICA M1 or M2	<345 min to randomisation	MM *vs* 3 mg intra-arterial tenecteplase	Early reperfusion (angiogram) or delayed reperfusion (perfusion imaging)
2BE3 (NCT06034847)	LVO and persistent distal occlusion	ICA, M1, M2, or basilar with persistent occlusion distal occlusion	NA	MM *vs* mechanical device or intra-arterial lytic	90-day mRS 0–2
Intra-arterial thrombolysis after successful EVT					
ANGEL-TNK (NCT05624190)	ICA, M1, M2, and eTICI 2b50–3; no IVT	ICA, M1, M2, and eTICI 2b50–3	4·5–24 h	MM *vs* 0·125 mg/kg intra-arterial tenecteplase (maximum 12·5 mg)	90-day mRS 0–1
ATTENTION IA[120] (NCT05684172)	Basilar, vertebral, P1, and eTICI 2b50–3	Basilar, vertebral, or P1	<24 h	MM *vs* intra-arterial tenecteplase	90-day mRS 0–1
ARTERIAL TNK BAO (NCT05580822)	Basilar and eTICI2b–3; no IVT	Basilar	<24 h	MM *vs* intra-arterial tenecteplase	90-day mRS 0–3
CHOICE-II (NCT05797792)	ICA, ACA, MCA, and mTICI 2b–3	ICA, ACA, or MCA	<24 h	MM *vs* intra-arterial alteplase	Microvascular hypoperfusion on CT perfusion at 36 h
EXTEND-AGNES TNK (NCT05892510)	ICA, M1, M2, and no IVT within 30 min of trial drug	ICA, M1, or M2	<24 h	Intra-arterial placebo *vs* 0·062mg/kg intra-arterial tenecteplase (maximum 6·25 mg)	Early neurological improvement (phase 2b) and 90-day mRS 0–2 (phase 3)
INSIST-IT[121] (NCT05657457)	Basilar and mTICI 2b–3	Basilar	<24 h	MM *vs* intra-arterial tenecteplase	90-day mRS 0–3
POST-TNK (ChiCTR2200064809)	ICA, M1 or M2, and eTICI 2c–3	ICA, M1, or M2	<24 h	MM *vs* intra-arterial tenecteplase (0·0625 mg/kg)	90-day mRS 0–1
POST-UK (ChiCTR2200065617)	ICA, M1 or M2, and eTICI 2c–3	ICA, M1, or M2	<24 h	MM *vs* intra-arterial urokinase (100 000 IU)	90-day mRS 0–1

ACA=anterior cerebral artery. AICA=anterior inferior cerebellar artery. eTICI=expanded treatment in cerebral ischaemia. EVT=endovascular therapy. ICA=internal carotid artery. IU=international units. IVT=intravenous thrombolysis. LVO=large vessel occlusion. MCA=middle cerebral artery. MeVO=medium or distal vessel occlusion. MM=medical management. mRS=modified Rankin Scale. mTICI=modified treatment in cerebral infarction. NA=not available. NIHSS=National Institutes of Health Stroke Scale. PICA=posterior inferior cerebellar artery. SCA=superior cerebellar artery.

Table 2: **Randomised or ongoing prospective trials**

without an increase in adverse events in the NBP group compared with placebo.[130]

Edaravone dexborneol (Simcere Pharmaceutical, Nanjing, China) is a neuroprotective drug with antioxidant and anti-inflammatory properties. In a phase 3 RCT of edaravone dexborneol or edaravone injection in patients presenting with acute ischaemic stroke within 48 h of symptom onset but not having reperfusion therapy, 90-day outcomes were more favourable in the edaravone dexborneol group (67·2% *vs* 59%; OR 1·42, 95% CI 1·12–1·81; p=0·004) than in the edaravone group.[133] A meta-analysis of randomised trials of edaravone dexborneol in ischaemic stroke indicated that edaravone might reduce neurological impairment.[134] A trial is

ongoing to study the potential benefit of edaravone dexborneol in a thrombectomy population (NCT05121883).

LVO with mild clinical severity

Approximately 4–8% of acute ischaemic stroke patients presenting with minor ischaemic stroke (defined as an NIHSS score of 5 or lower) harbour an LVO.[135,136] These patients present with mild neurological deficit that is probably related to leptomeningeal collaterals. Approximately 12% of patients who present with low-NIHSS score LVO are at risk for neurological deterioration, with higher rates in the presence of proximal LVO and long thrombus length.[137] Whether immediate endovascular therapy or deferred endovascular therapy is the optimal treatment for patients with LVO who present with low NIHSS scores is unknown. The TEMPO-2 randomised trial showed that intravenous tenecteplase had no benefit and possible harm in patients with acute ischaemic stroke presenting within 0–12 h of symptom onset, NIHSS 0 to 5, and an intracranial arterial occlusion.[138] Several trials are testing whether endovascular therapy confers benefit in patients with low NIHSS scores, including ENDOLOW (NCT04167527) and EXTREMIS-MOSTE (NCT03796468).

Patient selection

Altogether, patient selection for endovascular therapy can be summarised by clinical and imaging criteria with a minimalist approach based on the evolving randomised evidence. Most patients who present with an NIHSS score of higher than 5 and anterior circulation occlusion (eg, internal carotid artery, M1, and dominant M2), along with patients with an NIHSS of 10 or higher and basilar occlusion without extensive infarction (ie, small ischaemic core), are good candidates for endovascular therapy up to the 24 h window. These patients can be selected with NCCT and CT angiography alone.

In patients with a large ischaemic core (ASPECTS ≤5), trial evidence to date would support endovascular therapy up to 12 h with an ASPECTS of 3 or higher with NCCT for parenchymal selection based on the TENSION trial,[60] or with MRI ASPECTS of 0–5 in the 6·5 h window based on the LASTE trial.[59] In the 12–24 h window, patients can also be selected for endovascular therapy on the basis of imaging criteria of the SELECT2, ANGEL-ASPECT, and Japan RESCUE LIMIT trial criteria, which included perfusion imaging and MRI. Greater understanding of treatment benefit (or lack of it) will be gleaned across subgroups (eg, ASPECTS 0–2) with upcoming large core patient-level meta-analysis. A patient-centred approach, considering each patient's age, frailty, degree of pre-stroke disability, and quality of life, should be considered in the decision to treat on a case-by-case basis.

CT perfusion might serve as an aid to detecting MeVO,[139] but whether this warrants routine use of CT perfusion remains debatable; for example, we do not currently have evidence that knowledge of its presence would improve patient outcomes with an intervention (eg, endovascular therapy).[124,140,141]

Conclusion

A remarkable shift has occurred in the care of patients with LVO in the past decade. Advances from clinical trial data, endovascular therapy devices and techniques, expansion in the indication for endovascular therapy, and lowering of imaging barriers to endovascular therapy selection have improved our understanding of how to optimise the care of these patients. In this era of reperfusion, interest has been renewed in adjunctive brain cytoprotective strategies with endovascular therapy, now that likely prerequisite effective reperfusion can be achieved. Ongoing trials evaluating patients with low-NIHSS score LVO, MeVO, ICAD-related LVO, and adjunct intra-arterial thrombolysis or cerebroprotection might decrease neurological impairment related to acute ischaemic stroke with an arterial occlusion.

Contributors

TNN and MA conducted the literature search. MA and ZQ prepared the figures. TNN, MA, UF, ZQ, SN, H-SC, and ZM contributed to the writing of the Review with their assigned sections. TNN wrote the introduction, pathophysiology, small core early window, basilar artery, MeVO, concluding paragraphs, and drafted the tables. MA wrote the historical overview of technical aspects. ZM wrote the large core section. SN wrote the small core late window, and mild LVO section. UF wrote the bridging thrombolysis section. ZQ wrote the ICAD-LVO section. H-SC wrote the adjunctive therapy section. PK and TNN critically revised the manuscript draft.

Declaration of interests

TNN is a member of the advisory board for Aruna Bio and Brainomix; has received a research grant to institution from Medtronic; is the Associate Editor of Stroke; is a member of the data and safety monitoring committee of the SELECT2, TESLA, and ENDOLOW trials; is the President of Society of Vascular and Interventional Neurology; and is the co-principal investigator of the SUMMIT MAX and PICASSO trials. UF reports research support from the Swiss National Science Foundation and the Swiss Heart Foundation; reports research grants from Medtronic (for the BEYOND SWIFT and SWIFT DIRECT trials), Stryker, Rapid Medical, Penumbra, and Phenox (for the DISTAL trial); reports consultancies for Medtronic, Stryker, and CSL Behring; reports participation in an advisory board for Alexion/Portola, Boehringer Ingelheim, Biogen, and Acthera; is a member of a clinical event committee of the COATING study (Phenox) and a member of the data and safety monitoring committee of the TITAN, LATE_MT, and IN EXTREMIS trials; and reports presidency of the Swiss Neurological Society. All fees related to UF's declaration of interests are paid to institutions. UF is President-Elect of the European Stroke Organization. SN discloses stock options for Brainomix and was a speaker with Bayer, Boehringer Ingelheim, and Pfizer.
ZM was principal investigator of the the ANGEL ASPECT trial and discloses that the trial was supported by grants from Covidien Healthcare International Trading (Shanghai), Johnson & Johnson MedTech, Genesis MedTech (Shanghai), and Shanghai HeartCare Medical Technology that were made to the institution. PK was the principal investigator of an unrestricted grant for the investigator-initiated clinical trial, ENDOLOW, supported by Cerenovus; was the National Leader of the PACIFIC-Stroke clinical trial supported by Bayer; consulted for Lumosa and Basking Biosciences (for scientific advisory board participation); and was a one-time consultant for Shionogi. All other authors declare no competing interests.

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